**ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.**   EP 01 66 0136

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

31-10-2001

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 6120443	A	19-09-2000	FR	2747027 A1	10-10-1997
			CA	2251013 A1	16-10-1997
			EP	0892618 A1	27-01-1999
			WO	9737586 A1	16-10-1997
			JP	2000508191 T	04-07-2000
			NO	984687 A	03-12-1998
US 4788982	A	06-12-1988	EP	0232234 A2	12-08-1987
			SE	8600289 A	24-07-1987
US 5438983	A	08-08-1995	DE	4417610 A1	16-03-1995
			GB	2281780 A ,B	15-03-1995
EP 0774234	A	21-05-1997	JP	8322823 A	10-12-1996
			JP	8322824 A	10-12-1996
			JP	8322825 A	10-12-1996
			EP	0774234 A1	21-05-1997
			US	5871450 A	16-02-1999
			EP	0976361 A2	02-02-2000
			WO	9638087 A1	05-12-1996
			US	5964713 A	12-10-1999

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

European Patent
Office

EUROPEAN SEARCH REPORT

Application Number

EP 01 66 0136

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,A	US 6 120 443 A (COHEN-LAROQUE EMMANUEL-S) 19 September 2000 (2000-09-19) * column 3, line 59 - column 7, line 19; tables 1-5 *	1,11-14, 17	A61B5/11
A	US 4 788 982 A (GEDEON ANDRAS ET AL) 6 December 1988 (1988-12-06) * column 14, line 1 - line 55; table 2 *	1,13,14	
A	US 5 438 983 A (FALCONE RONALD) 8 August 1995 (1995-08-08) * column 3, line 27 - column 6, line 64; tables 1-6 *	1,9,10, 14	
A	EP 0 774 234 A (COLIN CORP) 21 May 1997 (1997-05-21) * column 5, line 52 - column 6, line 40; tables 1,2 *	1,13,14, 25	
A	KALAKUTSKY ET AL: "Anaesthesiological heart rate monitor" ENGINEERING IN MEDICINE AND BIOLOGY SOCIETY, 1995., IEEE 17TH ANNUAL CONFERENCE MONTREAL, QUE., CANADA 20-23 SEPT. 1995, NEW YORK, NY, USA,IEEE, US, 20 September 1995 (1995-09-20), page 723 XP010215590 ISBN: 0-7803-2475-7 * abstract * * page 723, left-hand column, line 1 - right-hand column, line 11 *	1,14	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61B G06F

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	31 October 2001	Weihs, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family. corresponding document
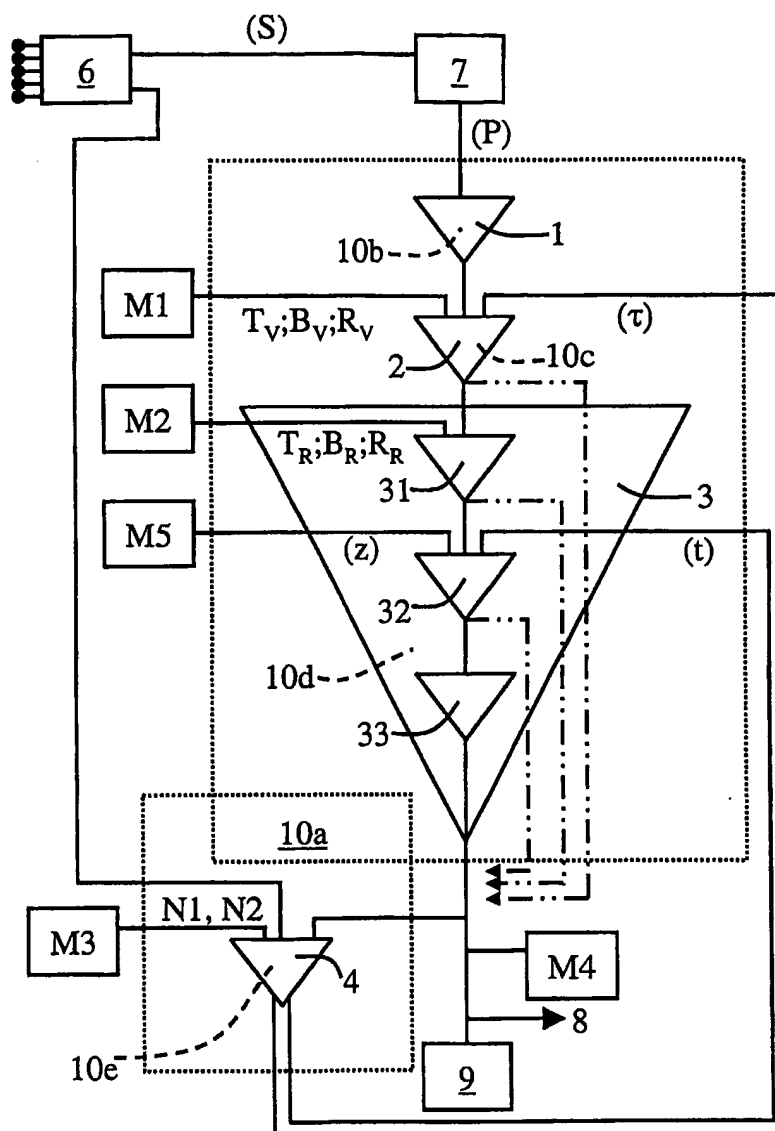
EPO FORM 1503 03.82 (P04C01)

Fig. 6

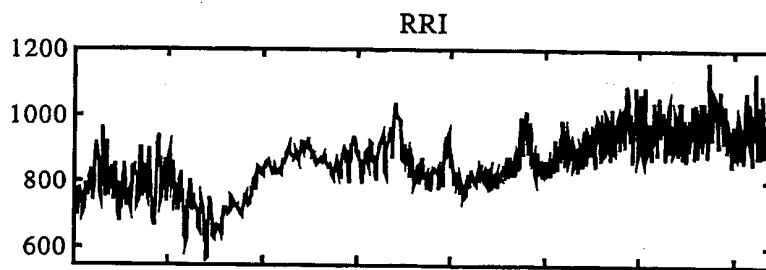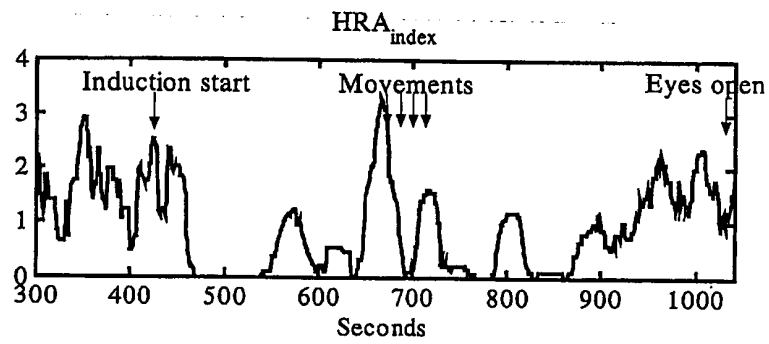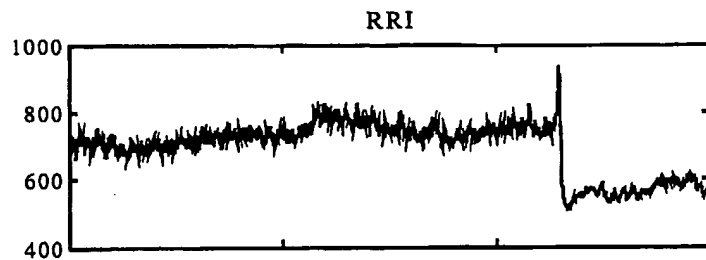RRI

Fig. 5A

HRA$_{index}$

Fig. 5B

RRI

Fig. 4A

Filtered RRI

Fig. 4B

Acceleration emphasised RRI

Fig. 4C

HRA$_{index}$

Fig. 4D

Seconds

Painful stimulus
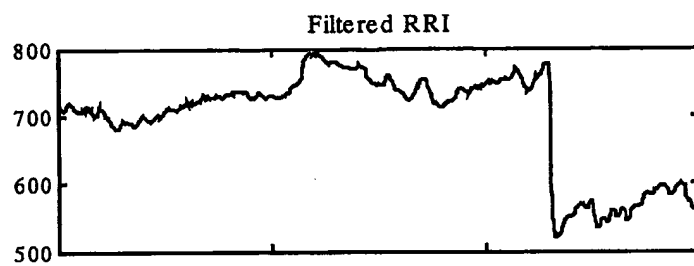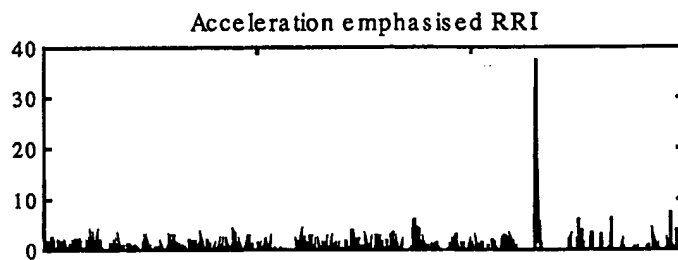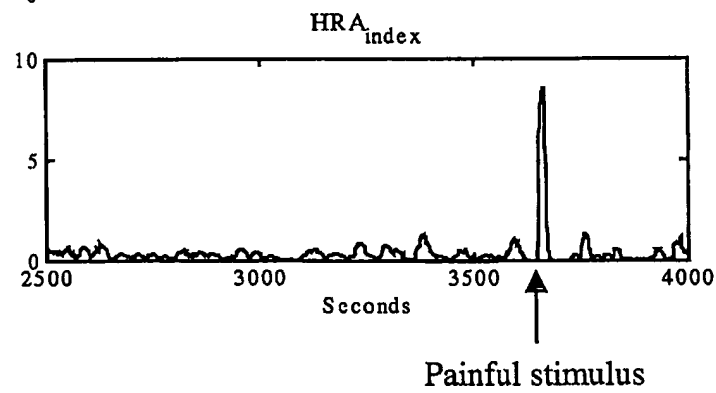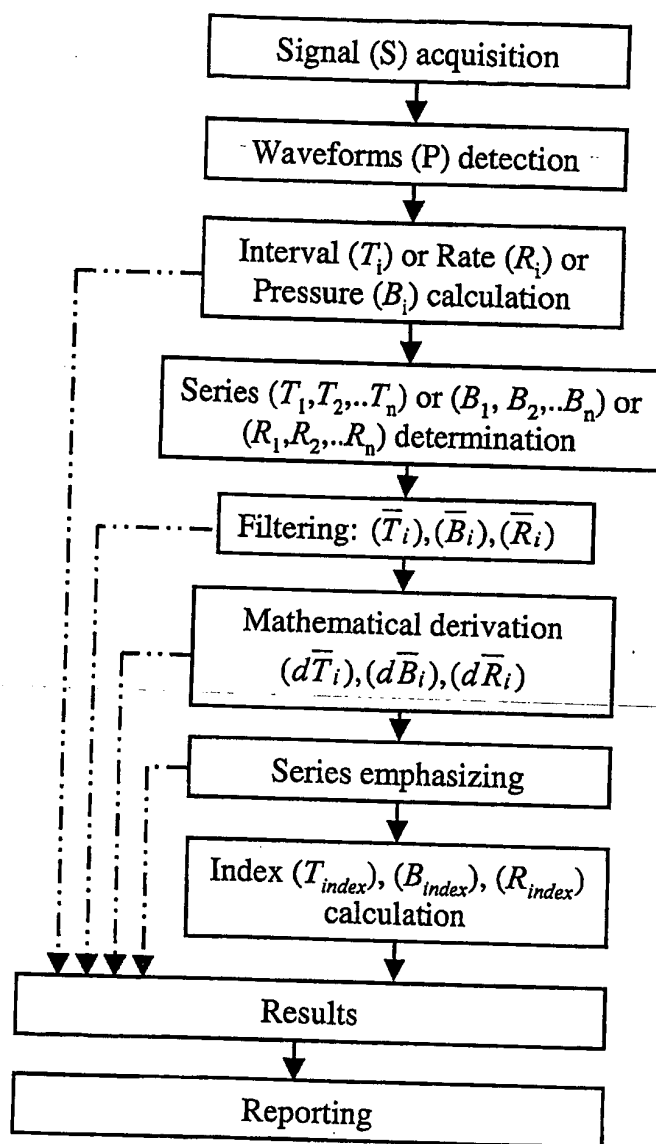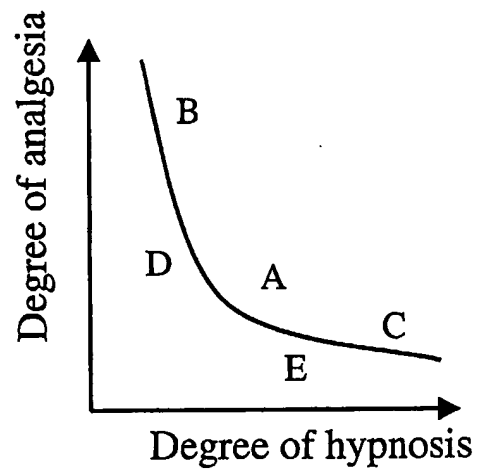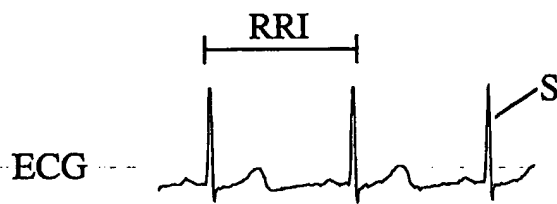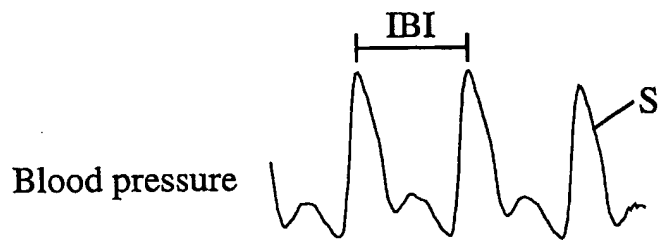
Fig. 3

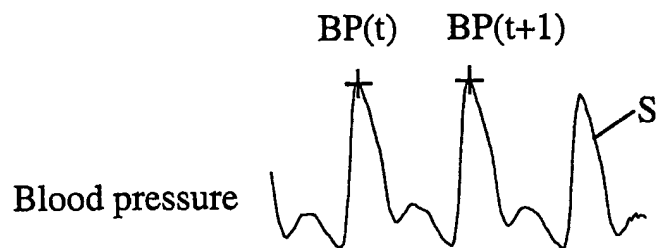Fig. 1

Fig. 2A

Fig. 2B

Fig. 2C

the operator.

16. A use according to claim 14 or 15, **characterized in that** said data of detection concerning analgesia is forwarded to the operator in form of:

  - temporally variable derivatives ($d\bar{T}_i$; $d\bar{B}_i$; $d\bar{R}_i$) decreasing ($d\bar{T}_i < 0$) of said time intervals (T_i), or increasing ($d\bar{R}_i > 0$; $d\bar{B}_i > 0$) of said temporal rates or pressures respectively; or
  - acceleration index (T_{index}; B_{index}; R_{index}) received from a selection of accelerations ($T_a(t)$; $B_a(t)$; $R_a(t)$) by a predetermined mathematical operation.

17. An apparatus for monitoring a condition of a patient under anaesthesia or sedation, the apparatus comprising:

  - detection means (6) for receiving a substantially continuous electrical signal (S) representing a cardiovascular activity of the patient;
  - a voltage/current dependent circuit (7) detecting each predetermined waveform (P) in said signal; and
  - first calculation means (1) providing at least one of the following - a series (T_1, T_2 ... T_{n-1}, T_n, T_{n+1} ...) of time intervals (T_i) between successive waveforms, or a series (B_1, B_2 ... B_n, B_{n+1} ...) of pressures (B_i), or a series (R_1, R_2 ... R_{n-1}, R_n, R_{n+1} ...) of temporal rates (R_i) from successive waveforms, **characterized in that** the apparatus further comprises:
  - second calculation means (2) providing successive average values ($\bar{T}_i$; $\bar{B}_i$; $\bar{R}_i$) of the series of said time intervals and/or said pressures and/or said temporal rates over a predetermined first time period (τ);
  - third calculation means (3) providing data about an decrease, or increase respectively in said successive average values; and
  - a display (9) and/or connections (8) into other devices.

18. An apparatus according to claim 17, **characterized in that** said third calculation means (3) comprises a first calculation unit (31) providing temporally variable derivatives ($d\bar{T}_i$; $d\bar{B}_i$; $d\bar{R}_i$) of said successive average values.

19. An apparatus according to claim 18, **characterized in that** said third calculation means (3) comprises a second calculation unit (32) applying a mathematical operator (Z) to said derivatives for providing a selection of accelerations ($T_a(t)$; $B_a(t)$; $R_a(t)$) including only those of said temporally variable derivatives ($d\bar{T}_i$; $d\bar{B}_i$; $d\bar{R}_i$) which are of a type or types predetermined as relevant and/or fulfil criteria of said type(s) under a second time period (t).

20. An apparatus according to claim 19, **characterized in that** said third calculation means (3) comprises a third calculation unit (33) applying a mathematical sliding sum of said selection of accelerations for providing an acceleration index (T_{index}; B_{index}; R_{index}).

21. An apparatus according to claim 17 or 19, **characterized in that** the apparatus further comprises fourth calculation means (4) connected to said detection means (6) and at least to the second calculation means (2) providing a first predetermined number (N1) of heart beats as the first time period (τ) into said second calculation means.

22. An apparatus according to claim 21, **characterized in that** said fourth calculation means (4) is further connected to the second calculation unit (32) of said third calculation means providing a second predetermined number (N2) of heart beats as the second time period (t) into said second calculation unit.

23. An apparatus according to claim 17, **characterized in that** said first calculation means (1), said second calculation means (2) and said third calculation means (3) are a single programmed processor (10a) or a combination of several programmed processors (10b, 10c, 10d, ...); or at least one of said first calculation means, said second calculation means and said third calculation means is a separate programmed processor.

24. An apparatus according to claim 21 or 23, **characterized in that** said fourth calculation means (4) is included in said single programmed processor (10a) or a combination of several programmed processors (10b - 10d) in a computer; or said fourth calculation means is a separate programmed processor (10e).

25. An apparatus according to claim 17, **characterized in that** it further comprises one or several memory means (M1, M2 ... M5) for storing at least the predetermined values (T_V; B_V; R_V; T_R; B_R; R_R) and/or the time periods (τ, t) or numbers (N1, N2) therefor and/or the mathematical operators (Z) and/or the results (T_{index}; B_{index}; R_{index}) of calculations.

3. A method according to claim 2, **characterized in that** said step of decrease/increase detecting further comprises: secondly, emphasizing those values of said derivatives which are decreasing ($d\bar{T}_i < 0$), or increasing ($d\bar{R}_i > 0$; $d\bar{B}_i > 0$) respectively; and that said emphasizing is performed by neglecting and/or suppressing those values of said derivatives which are not decreasing/increasing.

4. A method according to claim 3, **characterized in that** said neglecting and/or suppressing comprises applying a mathematical operator (Z) into said temporally variable derivative ($d\bar{T}_i$; $d\bar{R}_i$) to have a selection of decreasing/increasing accelerations ($T_a(t)$; $B_a(t)$; $R_a(t)$) describing the increase of the cardiovascular activity only.

5. A method according to claim 3, **characterized in that** said step of decrease/increase detecting further comprises: thirdly, performing said emphasizing over a predetermined second time period (t).

6. A method according to claim 5, **characterized in that** said emphasizing is performed by evaluating the selection of accelerations ($T_a(t)$; $B_a(t)$; $R_a(t)$), whereupon said selection provides an acceleration index (T_{index}; B_{index}; R_{index}) as a result; and that for said evaluation, a sliding sum of said selected accelerations ($T_a(t)$; $B_a(t)$; $R_a(t)$) over said second time period (t) is utilized.

7. A method according to claim 1, **characterized in that** said average value ($\bar{T}_i$; $\bar{B}_i$; $\bar{R}_i$) is a sliding even median or mean value of said time intervals (T_i) or pressures (B_i) or temporal rates (R_i), or a sliding weighted median or mean value of said time intervals (T_i) or pressures (B_i) or temporal rates (R_i) respectively calculated over said first time period (τ).

8. A method according to claim 6, **characterized in that** at least one of said acceleration indexes (T_{index} or B_{index} or R_{index}) is reported.

9. A method according to claim 1, **characterized in that** said decrease/increase in the plurality of successive average values ($\bar{T}_i$; $\bar{B}_i$; $\bar{R}_i$) is compared with a predetermined threshold change value (T_V; B_V; R_V); and that only values smaller/greater than said threshold value is forwarded for further calculations and/or for reporting and/or for an alarm is given in case said average values are smaller/greater than said threshold value.

10. A method according to claim 2 or 3 or 4, **characterized in that** said temporally variable derivatives ($d\bar{T}_i$; $d\bar{B}_i$; $d\bar{R}_i$) and/or said selection of accelerations ($T_a(t)$; $B_a(t)$; $R_a(t)$) are compared with one or several predetermined reference values (T_R; B_R; R_R); and that only values of the derivatives/accelerations being below, or exceeding respectively said reference value(s) are reported or forwarded to further calculations.

11. A method according to claim 1, **characterized in that** said predetermined first time period (τ) for said filtering is between 20 and 60 beats of heart.

12. A method according to claim 5, **characterized in that** said predetermined second time period (t) is between 20 and 120 beats of heart.

13. A method according to claim 1, **characterized in that** said step of acquiring signal (S) is performed by measuring electrical manifestations of cardiac actions (ECG), or a flow velocity or pressure of blood, or an absorption of electromagnetic radiation by blood, or acoustical manifestations emitted from blood-vascular system.

14. A use of a method in which a signal (S) representing a cardiovascular activity of a patient is analyzed for detection of periodically repeated waveforms (P), at least one of the following - time intervals (T_i) between, or pressures (B_i) from, or temporal rates (R_i) from successive waveforms are calculated to provide at least one of the following - a mathematical time series (T_1, T_2 ... T_{n-1}, T_n, T_{n+1} ...) of said time intervals, or a mathematical pressure series (B_1, B_2 ... B_n, B_{n+1} ...) of said pressures, or a mathematical rate series (R_1, R_2 ... R_n, R_{n+1} ...) of said temporal rates, **characterized in that** further for the use: said time series and/or pressure series and/or said rate series are mathematically filtered to provide a plurality of successive average values ($\bar{T}_i$; $\bar{B}_i$; $\bar{R}_i$) each over a predetermined first time period (τ), and a substantial decrease, or increase respectively in said average values is detected and data of said detection is forwarded to an operator for monitoring adequacy of analgesia of a patient under anaesthesia or sedation.

15. A use according to claim 14, **characterized in that** data describing muscle relaxation of said patient and/or data describing the loss of consciousness, together with said data of detection concerning analgesia, are forwarded to

signal of $\overline{RRI}_i$. A derivative of this signal, $d\overline{RRI}_i$, indicates changes in the HR level. A sign operator Z is then applied to pick up only HR accelerations:

$$RRI_a(t) = 0.5 \times d\overline{RRI}_i(t) \times \{Z \times [d\overline{RRI}_i(t)]\text{-}1\}, \qquad (I)$$

whereupon the sign operator Z means the following truth table:

$d\overline{RRI}_i(t)$	$Z =$
> 0	1
$= 0$	0
< 0	-1

$$(II)$$

HRA_{index} (= HR acceleration index) is then defined as a t-point running average of $RRI_a(t)$. The first length τ of the first mathematical filter or the second calculation means 2 is used to provide a proper type of data for emphasizing HR accelerations due to increase in the sympathetic activity. The second length t of the second mathematical filter or the third calculation means 3 is used to smooth the output signal HRA_{index} to be convenient for the use. The HRA_{index} effectively show any sympathetic reactions on HR during anaesthesia. Frequent and/or large reactions especially associated with potentially painful stimuli may be considered as a sign of insufficient analgesia.

[0035] In the apparatus according to the invention the first calculation means 1, the second calculation means 2 and the third calculation means 3 are preferably a single programmed processor 10a, but can alternatively be comprised of a combination of several programmed processors 10b, 10c, 10d, ... For example at least the first calculation means and/or the second calculation means and/or the third calculation means are/is a separate programmed processor. The fourth calculation means 4 can either be included in said single programmed processor 10a, or included in the combination of several programmed processors 10b - 10d, or the fourth calculation means can be a separate programmed processor 10e. In practice the one or several programmed processors 10a - 10e with the memories M1 - M5 are a computer. Components and parts as well as programs for such a computer are commercially available, and so the apparatus is not described more in detail.

Claims

1. A method for monitoring a condition of a patient under anaesthesia or sedation, the method comprising the steps of:

    - acquiring a signal (S) representing temporally a cardiovascular activity of the patient;
    - detecting periodically repeated waveforms (P) in said signal;
    - calculating at least one of the following - time intervals (T_i) between, or pressures (B_i) from, or temporal rates (R_i) from successive waveforms; and
    - forming at least one of the following - a mathematical time series (T_1, T_2 ...T_n, T_{n+1} ...) of said time intervals, or a mathematical pressure series (B_1, B_2 ...B_n, B_{n+1} ...) of said pressures, or a mathematical rate series (R_1, R_2, ...R_n, R_{n+1} ...) of said temporal rates,

    characterized in that the method further comprises the steps of:

    - filtering said time series and/or said pressure series and/or said rate series mathematically to provide a plurality of successive average values ($\overline{T}_i$; $\overline{B}_i$; $\overline{R}_i$) each over a predetermined first time period (τ); and
    - detecting a substantial decrease, or increase respectively in said plurality of successive average values.

2. A method according to claim 1, **characterized in that** said step of decrease/increase detecting comprises: firstly, a mathematical derivation of said plurality of successive average values ($\overline{T}_i$; $\overline{B}_i$; $\overline{R}_i$) to have temporally variable derivatives ($d\overline{T}_i$; $d\overline{B}_i$; $d\overline{R}_i$) thereof.

second calculation unit 32 applying this above mentioned mathematical operator Z to said derivatives, and a fifth memory means M5 for storing at least the mathematical operators Z if necessary. Accordingly the selection of accelerations $T_a(t)$ or $B_a(t)$ or $R_a(t)$ includes only those of said temporally variable derivatives $d\bar{T}_i$ or $d\bar{B}_i$ or $d\bar{R}_i$ respectively, which are of a type or types predetermined as relevant and/or fulfil criteria of said type(s) under a second time period

5   t. So a plurality of accelerations $T_a(t)$ to be further processed mathematically is a subset of the total set of variable derivatives $d\bar{T}_i$, and in a respective way a plurality of accelerations $R_a(t)$ to be further processed mathematically is a subset of the total set of variable derivatives $d\bar{R}_i$, and in a respective way a plurality of accelerations $B_a(t)$ to be further processed mathematically is a subset of the total set of variable derivatives $d\bar{B}_i$. These selections of accelerations T_a (t) or $B_a(t)$ or $R_a(t)$ may in some cases, e.g. for an experienced anaesthetist, be useful as such, as can be seen from

10   Fig. 4C. As an additional feature the respective one of the temporally variable derivatives $d\bar{T}_i$; $d\bar{B}_i$; $d\bar{R}_i$ and/or the respective one of the selections of accelerations $T_a(t)$; $B_a(t)$; $R_a(t)$ concerning time intervals or temporal rates can be compared with one or several predetermined reference values T_R; B_R; R_R, whereupon only those values of the derivatives or accelerations being below, or exceeding respectively said reference value(s) are reported or forwarded to further calculations. In the apparatus the third calculation means 3 or the second calculation unit 32 thereof is connected

15   to a second memory means M2 for storing at least the predetermined values T_R; B_R; R_R.

[0032]   Within this general step of decrease/increase detecting said emphasizing is thirdly performed over a predetermined second time period t using one or more of the following alternatives. According to one preferred alternative a sliding sum of said selected accelerations $T_a(t)$ or $B_a(t)$ or $R_a(t)$ over said second time period t is calculated, whereupon the respective one of the selections of accelerations $T_a(t)$; $B_a(t)$; $R_a(t)$ is in this way evaluated, which evaluation offers

20   an acceleration index T_{index} or B_{index} or R_{index} respectively as a final result. Figs. 4D and 5B illustrates the acceleration index R_{index}, in practice HRA_{index}, and it can be seen that both for the simple case - Fig. 4D - and for the more complicated case - Fig. 5B - acceleration index provides very clear and concise result, which is easy to understand. For this evaluation the predetermined second time period t is preferably between 20 and 120 beats of heart. According to another alternative the selection of accelerations $T_a(t)$ or $B_a(t)$ or $R_a(t)$ are compared with one or several predetermined

25   reference values T_R or B_R or R_R respectively, and only those values of the accelerations being below, or respectively exceeding said reference value(s) are reported as an acceleration index T_{index}; B_{index}; R_{index}. This last mentioned comparison can be utilized e.g. for an alarm, too. In the apparatus of the invention the third calculation means 3 comprises a third calculation unit 33 for applying the mathematical sliding sum of said selection of accelerations, or for comparing the acceleration with the reference values T_R or B_R or R_R. Anyway at least the respective one of the accel-

30   eration indexes T_{index}; B_{index}; R_{index} is reported. It is of course possible to report whichever intermediate results of calculations as shown in Fig. 3. For attaining the second time period t, which is dependent on the heart rate HR, the apparatus can utilize the fourth calculation means 4 disclosed earlier in this text, the fourth calculation means 4 being connected to the detection means 6 to receive the signal S and at least to the second calculation unit 32 of the third calculation means 3, whereupon the fourth calculation means 4 preferably feeds a second predetermined number N2

35   of heart beats as the second time period t into said second calculation unit 32. It is also possible to utilize a constant second time period t. The third memory means M3 connected to the fourth calculation means 4 stores the predetermined number N2 or the time period t according to what is needed.

[0033]   In the use of the inventive method, a substantial decrease, or increase respectively in said average values $\bar{T}_i$; $\bar{B}_i$; $\bar{R}_i$, and/or the temporally variable derivatives $d\bar{T}_i$; $d\bar{B}_i$; $d\bar{R}_i$, and/or more preferably the selection of accelerations

40    $T_a(t)$; $B_a(t)$; $R_a(t)$, and/or at least the acceleration index T_{index}; B_{index}; R_{index} are mathematically detected and data of said detection is forwarded to an operator for monitoring adequacy of analgesia of a patient under anaesthesia or sedation. Any of the above mentioned intermediate results as well as the final result - acceleration index or variable derivative - describes the change in cardiovascular activity and so serve as the detection of the decrease/increase in the plurality of successive average values, but the further the inventive calculations are proceeded the clearer and

45   more discernible any noticeable change is. Data describing muscle relaxation of said patient received from another system or part of the system, not disclosed in this text but exemplified e.g. in publication EP-0 691 105, and/or data describing the loss of consciousness from another system or part of the system, not disclosed in this text but exemplified e.g. in publication WO-01/24691, together with said data of detection concerning analgesia according to system, that is method or apparatus of the invention, are forwarded to the operator. Said data of detection concerning analgesia is

50   forwarded to the operator preferably in the form of an acceleration index T_{index} or B_{index} or R_{index} being larger than zero, which are the most clear and useful form. It is possible to forward also one or more of the intermediate results to the operator, e.g. temporally variable derivatives $d\bar{T}_i$ or $d\bar{B}_i$ or $d\bar{R}_i$ decreasing $d\bar{T}_i < 0$ of said time intervals T_i, or increasing $d\bar{R}_i > 0$ of said temporal rates, or increasing $d\bar{B}_i > 0$ of said pressures B_i respectively, or a selection of accelerations $T_a(t)$ or $B_a(t)$ or $R_a(t)$.

55   [0034]   Next an example is disclosed describing calculation of HRA_{index} statistic in practice. First, the electrocardiography (ECG) is monitored, and R-waves of the ECG QRS-complex are being detected. Beat-to-beat RRI_i (R-to-R Interval) signal is formed as a time difference of successive R-waves. Then, a median filter of length τ is applied on this signal to compute a data signal, which emphasises different HR levels in the RRI_i data signal, whereupon a data

or current dependent circuit 7 of the apparatus. Next either time intervals T_i between successive waveforms, or alternatively pressures B_i from successive waveforms, or alternatively temporal rates R_i from successive waveforms are calculated. The temporal rate R is actually a frequency and so an inverse value of time intervals T. The pressures B_i are dependent on the signal strength values. After at least two intervals/rates-calculation a mathematical time series T_1, T_2 ... T_n, T_{n+1} ... of said time intervals, or a mathematical pressure series B_1, B_2 ... B_n, B_{n+1} ...of said pressures, or a mathematical rate series R_1, R_2 ... R_n, R_{n+1} ... of said temporal rates are formed. The time span for calculating the temporal rates can be equal with the first time period discussed later, or any other time period. These calculations of time intervals T_i or pressures B_i or temporal rates R_i and arrangement into said series are performed by the first calculation means 1 of the apparatus. Figs. 4A and 5A illustrates graphically time series T_1, T_2 ... T_n, T_{n+1} ... in two different cases, in which the signals S are acquired from the RRI of an ECG. In this context it shall be mentioned that the pressure series of the blood pressure may be formed by using various different fiducial points in the blood pressure waveform, such as the systolic or diastolic pressure, their difference that is amplitude or pressure difference, any mean pressure or some other derivation of the successive pulses. The change from waveform BP(n) to the next waveform BP(n+1) is effectively the basis to the further calculations just like with calculations utilizing temporal rates and time intervals. In this text the definition 'pressure' means the values in any of the applicable fiducial points or any applicable pressure difference.

[0029] The method further comprises the step of filtering said time series or said rate series mathematically to provide a plurality of successive average values $\bar{T}_i$ or $\bar{B}_i$ or $\bar{R}_i$ each over a predetermined first time period τ, which calculation step is performed by second calculation means 2 of the apparatus. In this context, the definition average value means any type non-weighted or weighted value formed from a group of values and representing generally the whole group. Arithmetic mean values and median values are the most often used, generally known, and also practical for the purposes of the invention, but also geometric means or harmonic means etc. can be useful. The average values $\bar{T}_i$ or $\bar{B}_i$ or $\bar{R}_i$ are preferably sliding even medians or arithmetic mean values of the time intervals T_i or pressures B_i or temporal rates R_i, or sliding weighted medians or arithmetic mean values of the time intervals T_i or pressures B_i or temporal rates R_i respectively calculated over said first time period τ. This predetermined first filter length or first time period τ for the filtering is typically between 20 and 60 beats of heart to suppress non-sympathetic activity and hence emphasise sympathetic activity. For attaining the first time period τ, which is dependent on the heart rate HR, the apparatus further comprises fourth calculation means 4 connected to the detection means 6 to receive the signal S and at least to the second calculation means 2, whereupon the fourth calculation means 4 preferably feeds a first predetermined number N1 of heart beats as the first time period τ into said second calculation means 2. It is also possible to utilize a constant first time period τ. The fourth calculation means 4 is connected to a third memory means M3, which is storing at least the predetermined number N1 or the time period τ. For the examples as illustrated in Figs. 4B and 5B a median filter with length τ was used. Other filters such as finite impulse response filters with suitable characteristics might be used, too. The filtering using the first time period τ as disclosed above is a preferred embodiment, but alternatively the filtering can be performed also, or in combination with the preferred alternative, by comparing the time intervals T_i or pressures B_i or temporal rates R_i with a predetermined threshold value T_V; B_V; R_V with inclusion only values detected to be smaller, or greater respectively than said threshold value, whereafter the plurality of successive average values $\bar{T}_i$; $\bar{B}_i$; $\bar{R}_i$ is calculated. If necessary giving an alarm is possible in case the time intervals T_i or pressures B_i or temporal rates R_i are found to bee too low or high as compared to the threshold values. The apparatus further comprises a first memory means M1 connected to the second for storing at least the above mentioned predetermined values T_V; B_V; R_V.

[0030] An essential step in the method of invention is the detection of a substantial decrease, in case of time intervals T_i, or an increase, in case of temporal rate R_i or in case of pressure B_i of the plurality of successive average values $\bar{T}_i$; $\bar{B}_i$; $\bar{R}_i$, which is performed, generally speaking, by the third calculation means 3 of the apparatus. For this general step the average values $\bar{T}_i$ or $\bar{B}_i$ or $\bar{R}_i$ are firstly mathematically derived, whereupon temporally variable derivatives $d\bar{T}_i$ or $d\bar{B}_i$ or $d\bar{R}_i$ are received as intermediate results of the calculations. Derivations are processed e.g. by the first calculation unit 31 of the third calculation means 3, or in some other processor as is described later. These derivatives $d\bar{T}_i$; $d\bar{B}_i$; $d\bar{R}_i$ are a basic data about the decrease, or increase respectively of the successive average values. It is possible to feed the derivatives to a display 9 and/or connections 8 into other devices, but it is advantageous to continue calculation in order to have more clear data for evaluation.

[0031] In the general step of decrease/increase detecting those values of said derivatives which are decreasing $d\bar{T}_i < 0$, or increasing $d\bar{R}_i > 0$ and $d\bar{B}_i > 0$ respectively are secondly emphasized as follows. The emphasizing is performed by neglecting and/or suppressing those values of said derivatives, which are not decreasing/increasing at all, and/or not decreasing/increasing enough. Said neglecting and/or suppressing preferably comprises applying a mathematical operator Z into said temporally variable derivatives $d\bar{T}_i$ or $d\bar{B}_i$ or $d\bar{R}_i$ to have a selection of accelerations $T_a(t)$ or $B_a(t)$ or $R_a(t)$ describing the decrease of time interval derivatives $d\bar{T}_i$, or increase of temporal rate derivatives $d\bar{R}_i$ or increase of pressure derivatives $d\bar{B}_i$ each describing the increase of the cardiovascular activity only. Actually any predetermined mathematical operation capable of selecting more valid, that means a higher value with correct sign, derivatives $d\bar{T}_i$ or $d\bar{B}_i$ or $d\bar{R}_i$ from less valid derivatives can be useful. The third calculation means 3 of the apparatus can comprise a

describing sympathetic activity.

[0015] The statistic emphasising the potentially sympathetic reactions is calculated after above mentioned detection step. Preferably this is achieved by e.g. calculating a windowed sliding sum of the trend signal, which was formed in the previous step. Alternatively or in addition, a threshold may be used and only trend signals greater than the prede-

5 termined threshold are included. The statistic may also be normalised for example by setting the reference value to some well-defined period during the monitoring, or to some reference value obtained from larger studies.

[0016] The data concerning the detected decrease, or increase respectively of said average values, that is the emphasized data, is finally forwarded to an anaesthetist or other operator for monitoring adequacy of analgesia of a patient under anaesthesia or sedation. Further and according to requirements of operation also data describing muscle relax-

10 ation of said patient and/or data describing the loss of consciousness, together with the above described data of detection concerning analgesia, are forwarded to the operator. It is also possible to measure and receive signals S to provide two or all three of the variables discussed, that is time intervals and/or heart rates and/or pressures of cardiovascular activity and perform the respective calculations, and finally report the results or some of the intermediate results with or without their comparison to the anaesthetist/operator or to some other use. Most probable, if necessary,

15 is the measuring of pressures B_i and in addition either time intervals T_i or temporal rates R_i with respective further calculations, because the meanings of two latter time variables are in fact identical, while the meaning of pressure variables may be deviating. In any case at least one of these three signals is acquired and the respective variables T_i, or B_i, or R_i is calculated with further calculations and analysis.

[0017] The apparatus according to the invention is provided with proper detector(s) for receiving a substantially

20 continuous electrical signal S representing a cardiovascular activity of the patient, electrical circuits capable of detecting the predetermined points P in the signal, and proper calculation means, e.g. micro-processors, capable of performing the necessary calculations, as well as a display and/or connections for reporting those results and/or intermediate results of calculations needed. Useful components for the apparatus are commercially available, and so they are not described in detail.

25 **[0018]** The invention and its preferred embodiments are now described more in detail with reference made to the accompanying drawings.

[0019] **Fig. 1** describes the principle of interdependence between hypnosis and analgesia, whereupon the adequacy of another is dependent of the degree of the other.

[0020] **Figs. 2A - 2C** are schematic illustrations of the typical signals used for the invention and their functional

30 components for detecting waveforms and for determining time intervals or temporal rates of the heart function, in this case from ECG, or determining pressures of the heart functioning, in this case from blood pressure.

[0021] **Fig. 3** shows the main steps of processing or calculating the signal from measured ECG or blood pressure signals, as an example.

[0022] **Fig. 4A** is an example illustrating the time series of R-to-R Intervals (= RRI) sampled form an ECG signal

35 during sevoflurane anaesthesia and adenoidectomy in an 8-year-old child.

[0023] **Fig. 4B** illustrates the RRI data signal of Fig. 4A filtered according to one embodiment of the invention, the filter being a median filter with length of 40 heart beats.

[0024] **Fig. 4C** illustrates the data signal of Fig. 4B emphasized according to one embodiment of the invention, the filtered data signal being mathematically derived describing the acceleration of the change in RRI.

40 **[0025]** **Fig. 4D** illustrates the data signal of Fig. 4C after performing selection according to one embodiment of the invention, a windowed sliding summing of a length of 60 heart beats and further a mathematical sign operator being applied to the acceleration data, whereupon a HRA_{index} signal as the final result, which is forwarded to a display or to another device.

[0026] **Figs. 5A - 5B** are an example illustrating RRI signal and derived HRA_{index} signal during a short surgery.

45 Painful surgical stimulus causes movement responses, which are accompanied or even preceded by an increase in the HRA_{index}. Induction to anaesthesia causes the HRA_{index} to fall and awakening it to rise.

[0027] **Fig. 6** shows schematically the typical blocks of an apparatus according to the invention, the apparatus being capable of performing calculations for the intermediate results and final results illustrated in Figs. 4A to 4D and 5A to 4B, and according to the steps of the invention.

50 **[0028]** As already mentioned the method for monitoring a condition of a patient under anaesthesia or sedation comprises at first the step of acquiring a signal S representing temporally a cardiovascular activity of the patient. This acquiring can be performed using any method and any detection means 6 capable of receiving a substantially continuous electrical signal S corresponding the cardiac pulses of the patient in a useful form. The signal S is received by measuring electrical manifestations of cardiac actions like electrocardiography, or a flow velocity of blood, or pressure

55 of blood, or an absorption of electromagnetic radiation by blood, or acoustical manifestations emitted from blood-vascular system. The periodically repeated waveforms P, which are typically a predetermined type or section in a signal curve, for instance a specific point - R-wave, or any respective change in signal level, or any respective point providing a change in direction of the signal curve, e.g. a signal peak etc. - in said signal level is then detected by a voltage and/

plicates the identification of e.g. heart rate accelerations due to sympathetic activation. However, the time constants of the parasympathetic and sympathetic responses are different. For the former the response time is a few hundreds of milliseconds while for the latter the response starts only after a couple of seconds. Hence, it is possible to filter out short-term HRV primarily caused by parasympathetic activity, and hence emphasise the sympathetic activity in the signal. Furthermore, by picking up heart rate accelerations it is further possible to emphasise features, which are most potentially related to sympathetic activation. It should be noted that sympathetic reactions might be caused by other reasons than pain, such as physical exercise, mental stress, drugs, etc., too However, in anaesthetized or sedated subjects these other or external stimuli and factors, in addition to potential pain caused by surgery or care actions, are few and may be largely controlled by the care team. Though the reaction itself is not specific for pain and analgesia, it is possible to discriminate whether the identified reaction was due to pain or not by using this other information available for the care team. Hence, excluding the short-term effects of various drugs, the sympathetic reactions are potential markers for pain, and so concerning anaesthetized and sedated subjects, heart rate accelerations are potential markers for inadequate analgesia. The present innovation proposes a method to quantify the inadequate analgesia through one of the heart rate acceleration indexes and/or a blood pressure index, with the respective intermediates, too.

[0011] The present innovation comprises a step of acquiring at least one signal representing the subject's cardiac activity, a step of detecting the position of a waveform representing each single heart beat in the signal, a step of constructing a beat-to-beat signal by calculating the time difference or temporal rates like frequency of these waveforms, or alternatively a step of calculating the blood pressures of these waveforms, a step for filtering this signal to suppress non-sympathetic variations, a step for detecting potentially sympathetic reactions in the filtered signal, and a step for calculating a statistic related to the said potentially sympathetic reactions.

[0012] The signal S can be derived preferably from ECG but also from blood pressure, from blood flow velocity, from a light or other electromagnetic radiation absorption factor of blood, from oxygen content of the blood, from acoustic signal emitted by heart or from any other known or new signal or from any combination of the these signals or other known or new signals, which is dependent on cardiovascular activity of the patient and allows to determine a beat-to-beat property of the heart. As examples Fig. 2A shows a signal S received from ECG generally, and Figs. 2B and 2C show signals S received from blood pressure generally, and the other signals received from other kind of detections typically resemble these shown signals. In general, any signal, which would allow measuring sympathetic reactions, would do. Because the methods and apparatuses to acquire this kind of signals are generally known this step is not described more in detail.

[0013] Detecting the waveform P means finding a specific repeating point in the continuously variable signal acquired corresponding reliably and precisely enough to the beat-to-beat phenomenon or the pressure phenomenon of the heart so that the variable time between successive and similar or respective points of the signal, or the pressure difference between or the level in successive points of the signal can be established. A periodically repeated waveform P in the signal is so to be detected. There exist multitude of known and published methods to do this, and accordingly these methods are not described in detail. These methods include e.g. detection of a specific waveform present in the measured signal and representing a single heartbeat, such as R-wave in ECG, systolic pressure in blood pressure curve, maximum derivative in blood flow or blood pressure signal, etc. Furthermore, the methods include computing cross-correlation function of the signal and defining the inter-beat interval from the successive local maximums of the cross-correlation signal, and using a matched filter for the same purpose, etc. Preferably R-to-R interval (RRI) signal, generally the time interval T_i, which is calculated as a time difference between the successive R-waves, or a heart rate (HR), generally the temporal rate R_i, which is calculated as a frequency between the successive R-waves, is used, as shown in Fig. 2A. Respective time intervals T_i or temporal rates R_i can be determined on the basis of inter-beat-interval (IBI) defined from systolic pressure time instants in blood pressure signal, as shown in Fig. 2B, or the pressures B_i of the pulses on the basis of systolic blood pressure (BP) values in blood pressure signal, as shown in Fig. 2C, or any other known or new waveform. These calculated successive time intervals T_i form a mathematical time series $T_1, T_2 ... T_{n-1}, T_n, T_{n+1} ...$, and respectively these calculated successive temporal rates R_i form a mathematical rate series $R_1, R_2 ... R_{n-1}, R_n, R_{n+1} ...$, or these calculated successive pressures form a mathematical pressure series $B_1, B_2 ... B_{n-1}, B_n, B_{n+1} ....$

[0014] The time series and rate series respectively is then mathematically filtered to suppress signal components in the series caused by non-sympathetic activity, and hence to emphasize data corresponding sympathetic activity. In this step e.g. a plurality of successive average values $\bar{T}_i, \bar{B}_i, \bar{R}_i$ are formed from said time series or said rate series. Potentially sympathetic reactions in the filtered data signal can be detected as the shortening of e.g. the R-to-R-interval, or alternatively as the rise or increase of the HR-number, or as the increase of the blood pressure, i.e. the systolic pulses BP or any other levels or amplitudes, which processed data signal can be called a trend signal, which means signal components having a predetermined trend caused by sympathetic activity and so not suppressed. Preferably, only those parts related to potentially sympathetic reactions are restored, the other parts of the samples or time/rate series are suppressed e.g. by assigning them to zero. It shall be understood that there are several mathematical methods to suppress those samples not related to potentially sympathetic reactions and so to produce a trend signal

(EEG) signal have been introduced. The most well-known is the Bispectral Index (BIS), but also fractal spectrum, Lempel-Ziv complexity, Kolgomorov-Sinai entropy and spectral entropy etc. has been studied, e.g. Ira J. Rampil: "A Primer for EEG Signal Processing in Anesthesia" - Anesthesiology, Vol. 87, No. 4, Oct. 1998, and evidently some of them can provide a data describing reliably the level of consciousness independent of the individual. Muscle relaxation
5 may be measured e.g. by monitoring neuro-muscular transmission time and/or excited force, and one method and instrument for this purpose is disclosed in publication EP-0 691 105. Measuring muscle relaxation can be considered to be an established and reliable technology, and it is already a standard practice, because various devices are commercially available, too.

[0007] Accordingly the main object of the invention is to achieve a method and an apparatus for monitoring the
10 anaesthesia or sedation of a patient so that a reliable data about level or depth of analgesia would be available to an anaesthetist or to other purposes. The second object of the invention is to achieve a method and an apparatus for monitoring the anaesthesia or sedation capable of using measured signals derived from various sources of the patient, which means that the method should not be dependent on any single type of detector. The third object of the invention is to achieve a method and an apparatus for monitoring the anaesthesia or sedation capable to deliver such results
15 as an output, with the basis of which the adequacy of analgesia could be reliably enough assessed by inexperienced anaesthetists or other operators, too. The fourth object of the invention is to achieve a method and an apparatus for monitoring the anaesthesia or sedation functioning with an acceptable speed so that a change in analgesia to a hazardous direction is detected and reported early enough to allow timely corrective actions.

[0008] The above described problems can be solved and the above defined objects can be achieved by the inventive
20 method, which comprises filtering said time series and/or said pressure series and/or said rate series mathematically to provide a plurality of successive average values each over a predetermined first time period, and detecting a substantial decrease, or increase respectively in said plurality of successive average values; and by the inventive use, in which said time series and/or said pressure series and/or said rate series are mathematically filtered to provide a plurality of successive average values each over a predetermined first time period, and a substantial decrease, or
25 increase respectively in said average values is detected and data of said detection is forwarded to an operator for monitoring adequacy of analgesia of a patient under anaesthesia or sedation; as well as by the inventive apparatus, which comprises second calculation means providing successive average values of the series of said time intervals and/or said pressure series and/or said temporal rates over a predetermined first time period, third calculation means providing data about an decrease, or increase respectively in said successive average values, and a display and/or
30 connections into other devices.

[0009] The present innovation proposes a method, which enables monitoring a condition of a patient under anaesthesia or sedation, and specifically enables to assess the adequacy of analgesia in anaesthetized or sedated subjects in real time, based on the measurement of sympathetic reactions in beat-to-beat cardiovascular time series or pressure series or heart rate series. In anaesthesia there is a need to assess level of analgesia, i.e. adequacy of pain medication,
35 in order to avoid the subject to feel pain during the operation. This is a complicated task in presence of other medication, such as hypnotic agents and especially muscle relaxants. The invention functions successfully in solving this task and so fills the missing link in the complete anaesthesia monitoring. Especially for analgesia and hypnosis, the adequacy of another is dependent on the level of the other one as schematically shown in Fig. 1. In area D the degree or level of analgesia is acceptable as such, but the degree or level of hypnosis is quite too low, which case corresponds a local
40 analgesia or anaesthesia and is not practical in many cases. In area E the degree of hypnosis is acceptable as such, but the degree of analgesia is quite too low, whereupon the patient does not have consciousness during operation and does not remember anything about the operation afterwards, but the pain of the operation cause traumatic symptoms anyway. In area B the degree of analgesia is high enough so that a lower degree of hypnosis can be utilized, and in area C the degree of hypnosis is high enough so that a lower degree of analgesia can be utilized. In area A both the
45 analgesia and the hypnosis has optimal levels, but generally points on the right hand side of the curve in Fig. 1 are useful and points on the left hand side of the curve shall be avoided during total anaesthesia. For optimal total anaesthesia all the three components, that are analgesia, hypnosis and muscle relaxation should be controlled. This requires methods to independently assess all the components. This innovation is based on the facts that pain causes a sympathetic activation. Sympathetic activation propagates via sympathetic nervous branches to different sites of the body,
50 including heart and blood vessels. In blood vessels the activation causes vasoconstriction and increases hence blood pressure. In the heart sympathetic activation causes heart rate acceleration.

[0010] Actual heart rate is defined by the net effect of sympathetic and parasympathetic activity to the heart. An acceleration of heart rate may be caused either by sympathetic activation or withdrawal of parasympathetic activity, or both. A deceleration is caused if opposite changes in activity occurs. The amplitude or levels of the systemic arterial
55 blood pressure behave in an analogous way. A sudden increase of blood pressure is caused by the sympathetic activation, while a decrease is primarily caused by the decrease in the sympathetic activation - in case sudden changes in fluid balance can be excluded. Due to continuous modulation in both sympathetic and parasympathetic activity the beat-to-beat heart rate is continuously varied, which is called heart rate variability (HRV). The presence of HRV com-

4

Description

[0001] The present invention relates to a method for monitoring a condition of a patient under anaesthesia or sedation, the method comprising the steps of: acquiring a signal representing temporally a cardiovascular activity of the patient; detecting periodically repeated waveforms in said signal; calculating at least one of the following - time intervals between, or pressures from, or temporal rates from successive waveforms; and forming at least one of the following - a mathematical time series of said time intervals, or a mathematical pressure series of said pressures, or a mathematical rate series of said temporal rates. The invention also relates to a use of a method, in which a signal representing a cardiovascular activity of a patient is analyzed for detection of periodically repeated waveforms, at least one of the following - time intervals between, or pressures from, or temporal rates from successive waveforms are calculated to provide at least one of the following - a mathematical time series of said time intervals, or a mathematical pressure series of said pressures, or a mathematical rate series of said temporal rates, as well as to an apparatus for monitoring a condition of a patient under anaesthesia or sedation, the apparatus comprising: detection means for receiving a substantially continuous electrical signal representing a cardiovascular activity of the patient; a voltage/current dependent circuit detecting each predetermined waveform in said signal; and first calculation means providing at least one of the following - a series of time intervals between successive waveforms, or a series of pressures, or a series of temporal rates from successive waveforms.

[0002] Concept of the depth of anaesthesia has been of interest for recent decades, and several measures have been proposed to assess the depth of anaesthesia. Recently, however, this unitary anaesthesia theory of the existence of one-dimensional concept called "depth of anaesthesia" has been criticised as oversimplified. Instead it has been suggested that the anaesthesia has not one but three main components: hypnosis, analgesia and muscle relaxation. Different anaesthetic regimens have different effect on these three components. Furthermore, they have effects on both cortical and subcortical levels. An adequate anaesthesia means unresponsiveness to both noxious and non-noxious stimuli. The former may be defined by means of hemodynamic, motor and endocrine stability, while the latter is related to the loss of consciousness and recall and amnesia. In practice the adequate anaesthesia is administered by using a combination of drugs with different effects on brain, spinal cord, autonomic nervous system and neuromuscular junction. The combination of these effects hence creates the hypnotic, analgesic and muscle relaxing effects.

[0003] Heart rate (= HR) is controlled by autonomic nervous system. Especially sympathetic activation to the heart causes heart rate acceleration. Sudden pain causes a stress reaction, which is associated with sympathetic activation leading to sudden increase in HR and blood pressure. Hence, in clinical practise HR and blood pressure responses have been used for decades by experienced anaesthesiologists to heuristically detect inadequacy of anaesthesia. However, not only pain but also various other issues may cause variations in HR and blood pressure, and consequently the HR and blood pressure are continuously varying. Hence, monitoring just the mean level of HR and blood pressure is not sufficient.

[0004] Document US-5 372 140 proposes a method and an apparatus for providing a measure of the depth of anaesthesia based on analyzing beat-to-beat heart rate together with respiration. For that purpose a series of so-called R-waves from the cardiac signal is analyzed for determining the position in time of each R-wave relative to the respiratory cycle within which it occurs, and a measurement value representing the degree of clustering is derived. Further a so-called circular statistics is utilized with a test for randomness, and finally the measurement value is compared with a reference value to find the depth of anaesthesia. The proposed measure is related to respiratory sinus arrhythmia, which is primarily controlled by parasympathetic nervous system. The measure is poorly related to the functioning of the sympathetic nervous system, and hence may not measure sympathetic reactions to pain. As a conclusion, the disclosed method and apparatus does not provide results, which could be considered as an objective measure for the level of analgesia of a patient.

[0005] Document US-6 120 443 proposes another method and device for determining a depth of anaesthesia by acquiring a plurality of successive signals representing a cardiac activity of the patient, detecting a periodic wave therefrom, calculating time intervals between successive waves, determining a digital series of the time intervals, and calculating a fractal dimension of said series as well as calculating a depth of anaesthesia as a function of the fractal dimension. According to the document the signal is filtered by calculating the maximum correlation between the sampled signal and a theoretical signal, whereupon a signal period between 20 and 80 intervals is suggested, then regrouping the time intervals to form several digital series, and finally the fractal dimension is approximated by determining a dimension of correlation between said digital series, whereupon two to ten series is used. The disclosed method so is mathematically based on computing correlation dimension for beat-to-beat heart rate signal. Theoretically this kind of calculations requires a very long data sequence, leading to large delays in real-time monitoring. Though the inventor proposes to use relatively short data sequences to minimise the acquisition delay this makes the theoretical basis of the method questionable. As above, also this disclosed method and apparatus does not provide results, which could be considered as an objective or reliable measure for the level of analgesia of a patient.

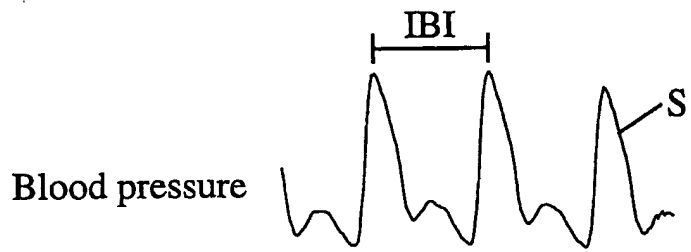[0006] Recently, methods for assessing the hypnotic component especially by monitoring electroencephalographic
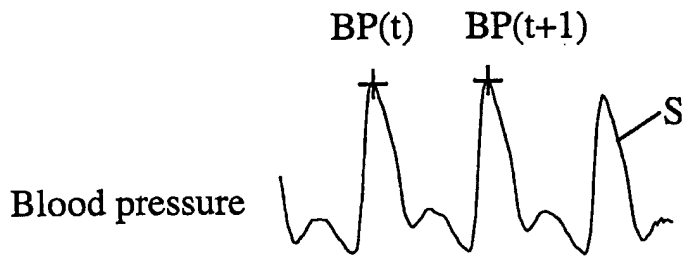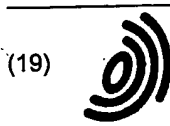
Fig. 2B

Fig. 2C

EUROPEAN PATENT APPLICATION

(12)

(71) Applicant: INSTRUMENTARIUM CORPORATION
00510 Helsinki (FI)

(72) Inventor: Korhonen, Ilkka
37560 Lempäälä (FI)

(74) Representative: Laako, Tero Jussi
Berggren Oy Ab
P.O. Box 16
00101 Helsinki (FI)

(54) **Monitoring a condition of a patient under anaesthesia or sedation**

(57) The invention relates to a method for monitoring a condition of a patient under anaesthesia or sedation. In the method a signal (S) is acquired representing a cardiovascular activity of the patient, and periodically repeated waveforms (P) are detected, followed by calculation of time intervals (T_i) between, and/or pressures (B_i) from, and/or temporal rates (R_i) from successive waveforms. Next at least one of the following - a mathematical time series (T_1, T_2 ... T_n, T_{n+1} ...), or a mathematical pressure series (B_1, B_2 ... B_n, B_{n+1} ...), or a mathematical rate series (R_1, R_2 ... R_n, R_{n+1} ...) is/are formed. Further in the method said time series and/or said pressure series and/or said rate series is mathematically filtered to provide successive average values ($\bar{T}_i$; $\bar{B}_i$; $\bar{R}_i$) over a predetermined first time period (τ), and a substantial decrease, or increase respectively in said average values is detected.

RRI

ECG

S

Fig. 2A

EP 1 273 265 A1